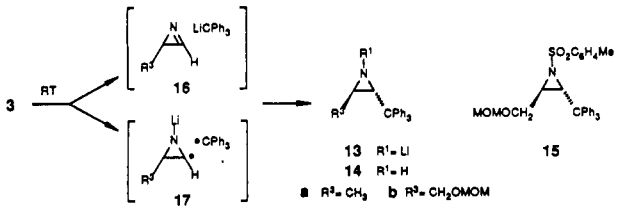
teristic $J_{2,3}$ = 6.1 Hz.[11,12] Similar coupling constants of ca. 6 Hz were eventually found in a number of the other trapping products **8**, all of which are assigned cis stereochemistry on the basis of the NMR data. Thus, **3** is configurationally stable due to the aziridine effect.[3c,10c] Finally, to establish synthetic utility, the ester **8b** (entry 6, Table I) was detritylated to give the corresponding N-H aziridine (80% yield) using formic acid in methanol at room temperature.[7c]

When **3b** was quenched with hexachloroethane, the 2-chloroaziridine **10** was obtained in good yield. Only a few isolated reports mention 2-chloroaziridines,[13] but they are relatively stable compared to other α-chloroamines. Thus, **10** survived rapid chromatography over silica gel. However, prolonged contact with the adsorbent (TLC, PLC) resulted in ring cleavage and formation of **6b**, probably via hydrolysis of the azirenium intermediate **11**. The same intermediate could also be trapped with Grignard reagents to give 2,3-disubstituted aziridines. Heating in THF was necessary to convert the chloroaziridine to **12**, and the trans diastereomers predominated (R^2 = Ph, 6.5:1 trans:cis, 64% isolated; R^2 = 1-naphthyl, 10:1 trans:cis, 71% isolated). These are the results expected from trapping of **11** from the less hindered face, and increased selectivity is observed with the more hindered naphthyl Grignard reagent.[14]

Based on the behavior of *C*-lithiooxiranes,[4,5] we had expected that thermal decomposition of **3** might lead to mixtures resulting from α-elimination or electrocyclic ring opening.[4,5] However, these reactions have not been detected. Instead, warming the pale orange **3a** or **3b** in THF above −10 °C produced a red color, and quenching at room temperature afforded a single major product in each case.[15] Since the product is an isomer of **9a** according to exact mass and contains the characteristic NMR signals of a *trans*-2,3-disubstituted aziridine ($J_{2,3}$ = ca. 3 Hz), it can only be **14**, the product of N-to-C trityl migration. This structure has been confirmed after tosylation of **14b** to afford **15**. The X-ray structure of this crystalline substance is shown in Figure 1.

We have been unable to find previous examples of anionic Stevens rearrangement involving trityl groups. There is one reported case of an anionic N-to-C migration of a benzyl group in the literature,[10b] as well as several other more distantly related nitrogen Stevens rearrangements.[16] There are also some indications that triarylmethyl can behave as an anionic leaving group.[17] This precedent suggests the hypothetical sequence from **3** to **16**, followed by recombination to give **13**. However, **16** is not intercepted by external butyllithium even if a 10-fold excess of the reagent is used for tin-lithium exchange. A caged radical-radical anion pair mechanism via **17** appears more likely from **3** to **13**.

Tin-lithium exchange succeeds with secondary α-aminoalkyllithium reagents $R_2NCH(R')Li$ if R′ can stabilize the C-Li bond by dipole[10c] or conjugation effects,[10d] but metal exchange usually fails when R′ = alkyl.[10e] The *C*-lithiated aziridines **3** are the first known exceptions to this rule, probably due to enhanced



s character in the exocyclic bonds. However, the enforced syn arrangement of C-Li and lone-pair orbitals may also be important and could be among the reasons why **3** is resistant to electrocyclic ring opening. Work is in progress to determine the role, if any, of nitrogen stereochemistry in the aziridine.

The methodology summarized above provides access to *cis*- or *trans*-2,3-disubstituted aziridines. We plan to evaluate enantiomerically pure *C*-lithioaziridines for applications in total synthesis.

Acknowledgment. This work was supported by the National Institutes of Health (CA17918). The authors also thank D. Powell for the X-ray structure of **15**.

Supplementary Material Available: Representative procedures and preparation of key intermediates (8 pages). Ordering information is given on any current masthead page.

(11) **9b**: colorless prisms from methanol, mp 114-116 °C; 200-MHz NMR ($CDCl_3$) δ 7.56-7.46 (6 H, m) 7.30-7.14 (9 H, m) 1.31 (3 H, d, *J* = 4.9 Hz) 1.26-1.15 (1 H, m) 1.04 (1 H, d, *J* = 5.9 Hz). **9d**: oil; 270-MHz NMR ($CDCl_3$) δ 7.52-7.47 (6 H, m) 7.30-7.16 (9 H, m) 4.62 (2 H, s) 3.90 (1 H, dd, *J* = 5.1, 10.4 Hz) 3.56 (1 H, dd, *J* = 6.1, 10.4 Hz) 3.34 (3 H, s) 1.52 (1 H, dt, *J* = 5.2, 6.1 Hz) 1.17 (1 H, d, *J* = 6.1 Hz).

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(14) For previous examples of chloroaziridine reactions with Grignard reagents, see ref 13c.

(15) For characterization of **14a** and **14b**, see supplementary material.

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Total Synthesis of the Marine Polypropionate (+)-Muamvatin. A Configurational Model for Siphonariid Metabolites

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Muamvatin,[1] isolated from the Fijian pulmonate mollusc *Siphonaria normalis*, is a novel marine polypropionate containing an unusual 2,4,6-trioxaadamantane ring system. Extensive NMR studies by Ireland et al.[1] allowed the partial structural assignment **1**, where the side-chain stereochemistry (C_{10}, C_{11})[2] could not be fully defined. We now report the first total synthesis of (+)-muamvatin, making use of efficient, substrate-based, aldol stereocontrol. This synthesis allows the complete assignment of the stereochemistry and leads to a general configurational model for this class of siphonariid metabolites.[3,4] We find that the trioxaadamantane ring system is readily produced by silica gel-promoted rearrangement, such that the muamvatin structure may well be an artifact of the isolation process.

Molecular modeling[5] of the four possible diastereomers of **1** allowed a prediction of the C_{10} relative stereochemistry (but not C_{11}).[6] Hence, we chose to first synthesize the aldehyde **2** with

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(2) We use a different numbering system for muamvatin from that used by Ireland et al.,[1] based on the likely polypropionate chain biosynthesis (Scheme III).

(3) (a) Denticulatins: Hochlowski, J. E.; Faulkner, D. J.; Matsumoto, G. K.; Clardy, J. *J. Am. Chem. Soc.* **1983**, *105*, 7413. (b) Siphonarins: Hochlowski, J. E.; Coll, J. C.; Faulkner, D. J.; Biskupiak, J. E.; Ireland, C. M.; Qi-tai, Z.; Cun-heng, H.; Clardy, J. *J. Am. Chem. Soc.* **1984**, *106*, 6748. (c) Baconipyrones: Manker, D. C.; Faulkner, D. J.; Stout, T. J.; Clardy, J. *J. Org. Chem.* **1989**, *54*, 5371.

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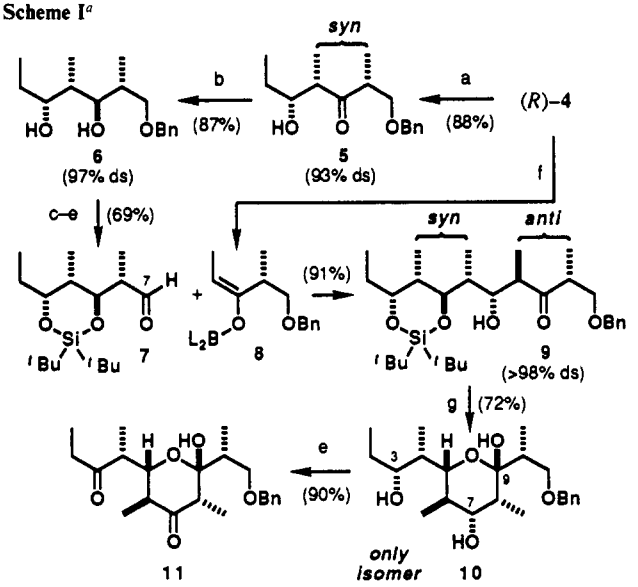
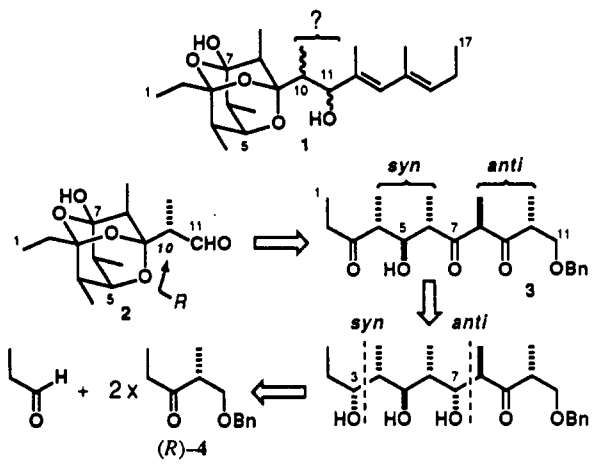
Scheme I[a]

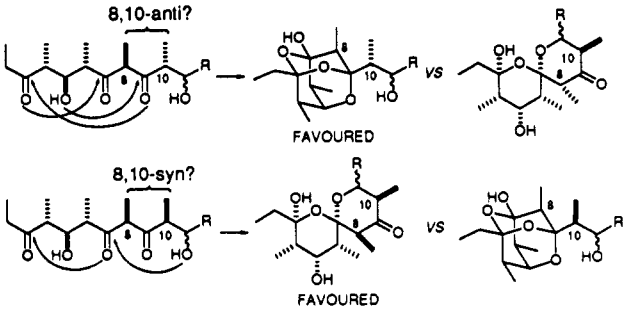


[a] (a) $Sn(OTf)_2$, Et_3N, CH_2Cl_2, −78 °C, EtCHO; (b) $Me_4NBH(OAc)_3$, MeCN, AcOH, −23 °C; (c) $^tBu_2Si(OTf)_2$, 2,6-lutidine, CH_2Cl_2, 20 °C; (d) H_2, 10% Pd/C, EtOH, 20 °C; (e) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, Et_3N, → −41 °C, aqueous NH_4Cl; (f) $(c\text{-}C_6H_{11})_2BCl$, Et_3N, Et_2O, −78 → −5 °C, 7, H_2O_2, pH 7 buffer, MeOH; (g) HF–pyridine, pyridine, THF, 20 °C.

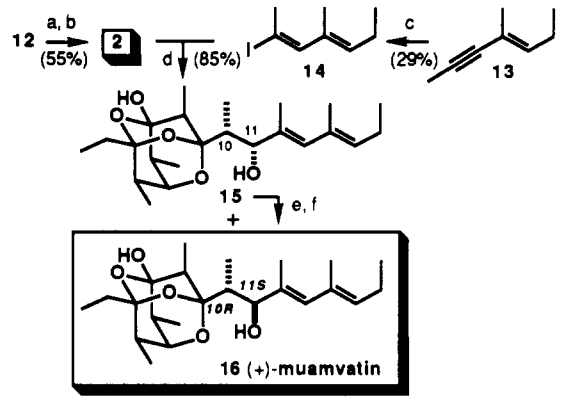
the 10*R* configuration, followed by elaboration into muamvatin. This aldehyde, having undefined absolute configuration and C_{10} stereochemistry, was previously obtained from oxidative degradation of muamvatin.[1] Starting from propionaldehyde, assembly of an appropriate open-chain precursor (**3**) requires two sequential aldol chain extensions by the dipropionate reagent (*R*)-**4**.[7,8]



(6) The reported ^1H NMR vicinal coupling constant between H_{10} and H_{11} of $J = 9.02$ Hz[1] suggested a preferred dihedral angle of around 180° in muamvatin, which was more consistent with the energy-minimized conformations calculated for **15** and **16** than for the epimeric 10*S* compounds. This was also supported by consideration of the calculated energies of the available cyclization products, where **17** having 8,10-anti vs 8,10-syn stereochemistry was predicted to cyclize in the muamvatin and siphonarin modes, respectively.



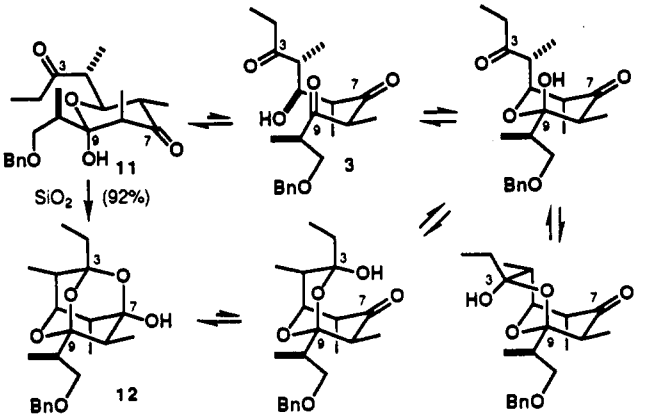
Scheme II[a]



[a] (a) H_2, 10% Pd/C, THF, 20 °C; (b) PDC, 4-Å molecular sieves, CH_2Cl_2, 20 °C; (c) catecholborane, 70 °C, chloramine-T, NaI, aqueous THF, 0 °C; (d) ^{n}BuLi, THF, −78 °C, **2**; (e) $^nPr_4NRuO_4$, NMO, CH_2Cl_2, 20 °C; (f) DIBAL, Et_2O, −78 °C.

Addition of the Sn(II) enolate, obtained by enolization of (*R*)-**4** with $Sn(OTf)_2/Et_3N$, to propionaldehyde gave the syn-syn[8a,d] aldol isomer **5** (Scheme I) with 93% diastereoselectivity (ds) and 88% yield. Using $Me_4NBH(OAc)_3$,[9] reduction to the corresponding anti 1,3-diol **6** proceeded well (97% ds), which was then protected as its di-*tert*-butylsilylene ether, debenzylated, and Swern oxidized to give the aldehyde **7** (60% from **5**). The second dipropionate aldol addition employed the (*E*) enol dicyclohexylborinate **8**, which was added to **7** to give exclusively the anti-anti[8e-g] isomer **9** in 91% yield. Removal of the silicon protecting group under mild conditions (HF, pyridine)[8f] then gave the hemiacetal **10** as the only product (72%). This served to protect the 9-OH in the subsequent Swern oxidation step, giving **11** (85%), the immediate precursor of the desired trioxaadamantane ring system.

The rearrangement **11** → **12** requires ring-opening to give the hydroxy triketone **3**, followed by a series of acetal ring forming steps as shown. Initial attempts to achieve this using acid catalysis



led only to dehydration across C_8 and C_9. In contrast, simple treatment with chromatography grade silica gel allowed the efficient transformation of **11** into **12**. The hemiacetal **11** was absorbed on to silica gel (Merck kieselgel 60 F_{254}) and then eluted off after 18 h to give the trioxaadamantane **12** in 92% yield. Debenzylation and PDC oxidation (Scheme II) then gave the aldehyde **2** in 55% yield, with spectroscopic data (^1H, ^{13}C NMR,

(7) Prepared in 3 steps from (*R*)-methyl 3-hydroxy-2-methylpropionate (Aldrich), see ref 8b.

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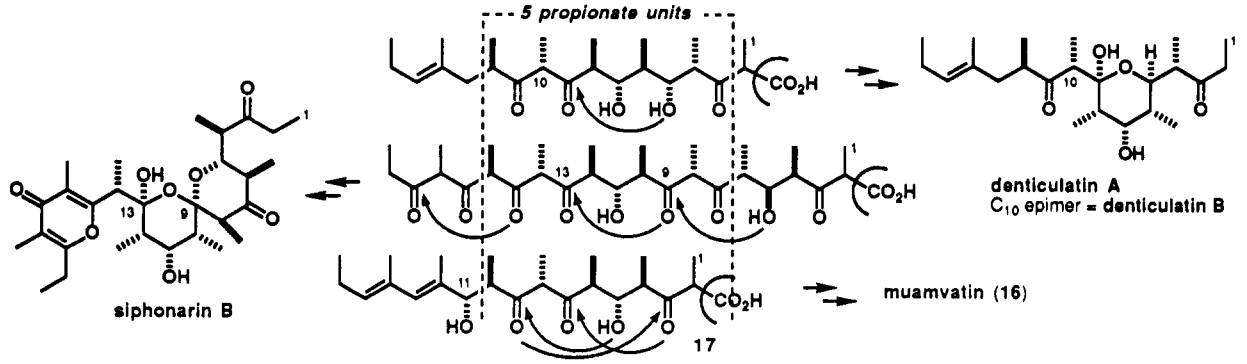
Scheme III. Configurational Model for Siphonariid Metabolites



IR) identical[10] to that reported by Ireland et al.,[1] thus establishing the C_{10} relative stereochemistry. Comparison of optical rotation, $[\alpha]^{20}_D = +84.4°$ (*c* 0.9, CH_2Cl_2) for **2** vs lit.[1] $[\alpha]^{20}_D = +50.2°$ (*c* 0.09, CH_2Cl_2), indicated that we had prepared[11] the correct enantiomer for completing a total synthesis of (+)-muamvatin.

The light-sensitive iodide **14** was prepared from the enyne **13**[12] by regioselective hydroboration by catecholborane, followed by treatment with in situ generated ICl.[13] Lithium–iodine exchange (^{n}BuLi) gave the corresponding dienyl lithium, which was then added to the aldehyde **2**. The resulting alcohol mixture (85% yield) was chromatographed (SiO_2, 5% Et_2O/CH_2Cl_2) to give predominantly 11-*epi*-muamvatin ($R_f = 0.19$) and a small amount (5%) of muamvatin ($R_f = 0.15$). ^{1}H NMR analysis of both the (*R*)- and (*S*)-MTPA esters of 11-*epi*-muamvatin showed that it had the 11*R* configuration, i.e., **15**.[14] This alcohol **15** could be oxidized to the corresponding dienone using catalytic $^n Pr_4NRuO_4$,[15] followed by stereocontrolled reduction by DIBAL. This now gave (+)-muamvatin as the sole product, $[\alpha]^{20}_D = +62.0°$ (*c* 0.08, CH_2Cl_2) vs lit.[1] $[\alpha]^{20}_D = +61.1°$ (*c* 0.175, CH_2Cl_2), in 14 steps and 89% ds from (*R*)-**4**. The ^{1}H and ^{13}C NMR spectra were in full accord with the published data[1] and spectra provided by Professor Ireland. On the basis of the Mosher ester analysis on **15** and Felkin–Cram control operating in both the DIBAL reduction step and aldehyde addition (**14** + **2** → **15**), we assign the structure **16** (10*R*, 11*S*) to muamvatin.

The stereochemical homology between muamvatin and related siphonariid metabolites[3b,c] can be seen from the biogenetic configurational model[4b,16] in Scheme III, where a common pentapropionate section is apparent. The ready production of the trioxaadamantane skeleton by silica gel treatment suggests that muamvatin is probably an artifact of the chromatographic purification used in the natural product isolation.[17] On isolation, the cyclization mode is presumably under thermodynamic control and can be predicted[6] from the oxidation state of the carbons and the configuration of the hydroxyl and methyl groups in the associated acyclic precursor **17**.

Acknowledgment. We thank the SERC for support (Postdoctoral Award to M.V.P.; grant GR/F73458), Dr. J. M. Goodman (Cambridge) for the molecular modeling results, Dr. M. J. Garson (Queensland) for helpful discussions, Professor R. W. Hoffmann (Marburg) for the exchange of information, and Professor C. M. Ireland (Utah) for kindly providing spectra of muamvatin and the degradation product **2**.

Supplementary Material Available: Listing of spectroscopic and physical data for all numbered compounds (5 pages). Ordering information is given on any current masthead page.

(10) In (+)-**2**, the ^{13}C NMR resonances for the acetal carbons appear at δ 103.1, 102.9, and 97.3, whereas these are reported[1] at δ 105.4, 103.1, and 97.2. Professor Ireland informs us that δ 105.4 is an error and there are two signals at 103.1 and 102.9 ppm. Otherwise, the NMR data were identical. In our hands, (+)-**2** was obtained as a crystalline solid, mp 153–154 °C (pentane).

(11) We initially prepared the enantiomer of aldehyde **2**, which had $[\alpha]_D^{20} = -80°$ (c 0.05, CH_2Cl_2), by using the (*S*) ketone corresponding to **4**.

(12) Prepared in two steps from (*E*)-2-methyl-2-pentenal in 58% yield by: (i) PPh_3, CBr_4, CH_2Cl_2, 0 °C; (ii) ^{n}BuLi, THF, −78 → 20 °C, MeI, −78 → 20 °C. Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.

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(17) This may also be true for other siphonariid metabolites,[3,8f] where the actual natural products are more closely related to the open-chain polypropionate precursors.

Base Properties of CH_3NC: Interactions with HCl and H^+ and Comparisons with CH_3CN

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In a recent paper, Legon, Lister, and Warner reported an elegant study of the hydrogen-bonded complex formed between CH_3NC and HCl.[1] On the basis of the rotational spectra of three isotopomers, they determined that the complex $CH_3NC\cdots HCl$ has C_{3v} symmetry with an intermolecular C–Cl distance of 3.404 Å, which is longer than the experimental N–Cl distance of 3.291 Å in $CH_3CN\cdots HCl$.[2] From their data they also suggested that these two complexes might have similar stabilities even though the proton affinity of CH_3NC is significantly greater than that of CH_3CN.[3]

The methodological dependence of the structures and binding energies of acid–base complexes has been a subject of continuing interest in this laboratory. As part of that study, the structures and binding energies of a series of hydrogen-bonded complexes including $CH_3CN\cdots HCl$ were investigated at a high level of ab initio theory, and good agreement between computed and experimental data was found.[4] In the present communication, this same level of theory will be used to investigate the complex $CH_3NC\cdots HCl$. Comparisons will be made of the structures and binding energies of $CH_3NC\cdots HCl$ and $CH_3CN\cdots HCl$ and of the proton affinities of the isomers CH_3CN and CH_3NC.

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